SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Total Prostate Specific Antigen (Total PSA)
Device Trade Name:	VIDAS TPSA assay
Applicant's Name and Address:	bioMerieux, Inc. 595 Anglum Drive Hazelwood, MO 63042-2320
Date(s) of Panel Recommendation:	In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.
Premarket Approval Application (PMA) Number:	P040008
Date of Notice of Approval to Applicant:	July 8, 2004

II. INDICATIONS FOR USE

VIDAS TPSA is intended for use with a VIDAS (VITEK ImmunoDiagnostic Assay system) instrument as an automated enzyme-linked fluorescent immunoassay (ELFA) for the quantitative measurement of total prostate specific antigen in human serum. The VIDAS TPSA is indicated as an aid in the management of patients with prostate cancer and as an aid in the detection of prostate cancer in conjunction with digital rectal examination (DRE) in men age 50 years or older. Prostate biopsy is required for diagnosis of prostate cancer.

III. CONTRAINDICATIONS

None known

IV. WARNINGS AND PRECAUTIONS

Warnings, precautions, and limitations can be found in the labeling.

V. DEVICE DESCRIPTION

The assay is an automated enzyme-linked immunoassay using a fluorescence signal for the quantitative measurement of total PSA in human serum. The assay is designed for use on the VIDAS or mini-VIDAS instrument using a two-step sandwich immunoassay with fluorescence detection of signal. A solid phase receptacle with antibody to PSA coated onto the surface captures total PSA present in the sample and serves as pipetting device. Reagents for the assay are ready-to-use and pre-dispensed in sealed reagent strips. Sample is cycled into the solid phase receptacle several times to allow capture of PSA in the sample. Unbound components are removed during washing steps. Alkaline phosphatase labeled anti-PSA antibody binds to captured PSA in the second step. Unbound conjugate is removed during washing steps. The substrate, 4-methyl-umbelliferyl phosphate, is converted to a fluorescent product, 4-methyl-umbelliferone, which is measured at 450 nm wavelength. The intensity of fluorescence is proportional to the amount of captured PSA in the sample. Assay calibrators are included in the kit to which the amount of released flourescence is related in the assay run. At the end of an assay run, the amount of PSA is calculated by the instrument automatically using the calibration curve stored in memory. The kit is composed of 60 solid phase receptacles and reagent strips containing all necessary materials for the assay.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Alternative practices and procedures for aiding in the detection of prostate cancer include physical examination using digital rectal examination (DRE) and diagnostic imaging by transrectal ultrasound (TRUS). Confirmation of prostate cancer is determined by biopsy.

Other devices for measuring serum total PSA are commercially available to aid in the detection of prostate cancer in conjunction with DRE in men aged 50 years and older.

VII. MARKETING HISTORY

The bioMerieux VIDAS® TPSA assay is CE marked and was orginially introduced into the European market for diagnosis of prostate disorders (including cancer of the prostate) and for the prognosis of patients with diagnosis and malignent tumors.

It has been marketed in the United States, the VIDAS® TPSA assay since 2001 an aid in the management of patients with prostate cancer for use with a VIDAS (VITEK ImmunoDiagnostic Assay System) instrument as an automated enzyme-linked fluorescent immunoassay (ELFA) for the quantitative measurement of total prostate specific antigen in serum.

The product has been marketed in Europe, Latin America, North America, and Asia Pacific for the indication that is the subject of this PMA since 2003.

The product has not been withdrawn from the market for reasons related to safety or effectiveness.

VIII. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

When the device is used according to the instructions provided, accurate assay results should be obtained. A falsely elevated PSA value could lead to an unnecessary biopsy. A falsely low PSA value could delay recognition of the presence of prostate cancer by the physician and could adversely delay the initiation of therapy.

The PSA value is not diagnostic for prostate cancer. It should be used in conjunction with symptoms, clinical evaluation, digital rectal examination, and other laboratory tests or imaging techniques. If the PSA value is inconsistent with clinical evidence, additional testing is suggested to confirm the result. Confirmation of prostate cancer can only be determined by prostatic biopsy.

IX. SUMMARY OF PRECLINICAL STUDIES

New non-clinical studies were not performed. The submission sought an additional Indication for use only. The assay method has not been altered since original clearance for the initial Indication for use (K010550).

X. SUMMARY OF CLINICAL STUDIES

A. Study objectives

Studies were conducted by a contract research organization between November 1999 and November 2000 in support of the Intended Use. The stated objectives are the following:

- Assess clinical validity by the use of clinical sensitivity and specificity as measured by the device alone and in conjunction with DRE results. The added value of total PSA over DRE alone is assessed.
- Assess clinical reliability using positive and negative predictive values as measured by the device alone and in conjunction with DRE result.
- Determine the 95th order statistic of total PSA (tPSA) in a cohort of apparently healthy men aged 50 years of age or older.
- Determine the distribution of results in an apparently healthy cohort to support a threshold of 4.0 ng/ml.

B. Patient inclusion/exclusion criteria

Serum samples were obtained from men, regardless of race, presenting to a practicing urologist with symptoms leading to evaluation for cancer, including trans-rectal biopsy meeting the following criteria:

1. No history of benign prostate disease 6 months prior to referral
2. No history of an evaluation for prostate cancer prior to referral
3. Age 50 years old or older

Subjects meeting the following criteria were excluded:

1. Men younger than 50 years of age
2. Men with prior history of or treatment for prostate cancer
3. Men with a history of treatment for benign prostate disease less than 6 months prior to referral
4. Subject has undergone DRE or other forms of prostate manipulation less than 5 days prior to sample draw

Serum samples were obtained from apparently healthy men visiting community family practice physicians, under an IRB collection protocol, meeting the following criteria:

1. Healthy individual having no fever or infections, meeting criteria for blood bank donation and who has no known prostate disease or history of prostate disease

2. Known age

3. Was entered into the study only once

4. Whose serum sample was stored at or below -70°C for no longer than 3 years

5. Smoking/non-smoking status was known

Apparently healthy individuals not meeting the inclusion criteria were excluded.

C. Sample handling and testing

For evaluated patients, a sample was defined as a blood serum specimen collected by venipuncture no more than 15 days prior to prostate biopsy and more than 5 days post prostate manipulation. Serum was collected in serum separator tubes, allowed to clot for a maximum of 45 min and centrifuged for 15 minutes. Serum was shipped to the testing laboratory. Sample was aliquoted and stored at -80°C. For normal healthy adults, serum was collected by venipuncture in serum separator tubes, allowed to clot for 45 minutes and centrifuged for 15 minutes. Serum was shipped to the testing facility and stored at -70°C until tested.

Serum samples were tested on the VIDAS instrument using VIDAS tPSA assay reagents. Samples were idenitified by sample number to mask clinical status of the subjects. Investigators were masked to the PSA values used in the data analysis.

D. Sample size

Samples were retrospectively obtained serum specimens from 700 subjects collected from 34 clinical sites in the United States obtained under an IRB approved protocol with informed consent. Four hundred apparently healthy men aged 50 years of age or older meeting Red Cross criteria for blood donation and having no known prostate disease or history of prostate disease supplied samples.

E. Results

1. General patient demographics and results

The overall cancer rate was 33.6%. The cancer rate ranged from 0% to 90% by site. The overall average age by site was 66.6 years (95% confidence interval 66.0 to 67.2 years). The mean age by site ranged from 62.5 years to 73 years. Of 700 subjects in the patient cohort, 82% were Caucasian, 13% African American, 3% Hispanic, and 1.4% other races.

Of all subjects, 19% had a DRE result the physician considered suspicious for cancer. Twenty-five percent (25%) of subjects had a DRE result the physician considered not suspicious for cancer but abnormal. Forty-five percent (45%) of subjects had a normal DRE result. Ten percent (10%) of subjects had a DRE result listed as other. DRE results were combined into 2 categories (abnormal and normal) by combining physician categorizations "suspicious for cancer" and "other" into the abnormal category. The other binary category for DRE combined physician categorizations "not suspicious for cancer" and "normal" into the normal category. Therefore, 207 of 700 subjects (29.6%) were categorized as having an abnormal digital rectal examination and 493 subjects (70.4%) were categorized as having a normal digital rectal examination.

The following table shows the subject count and percentage of total subjects with the designated biopsy results:

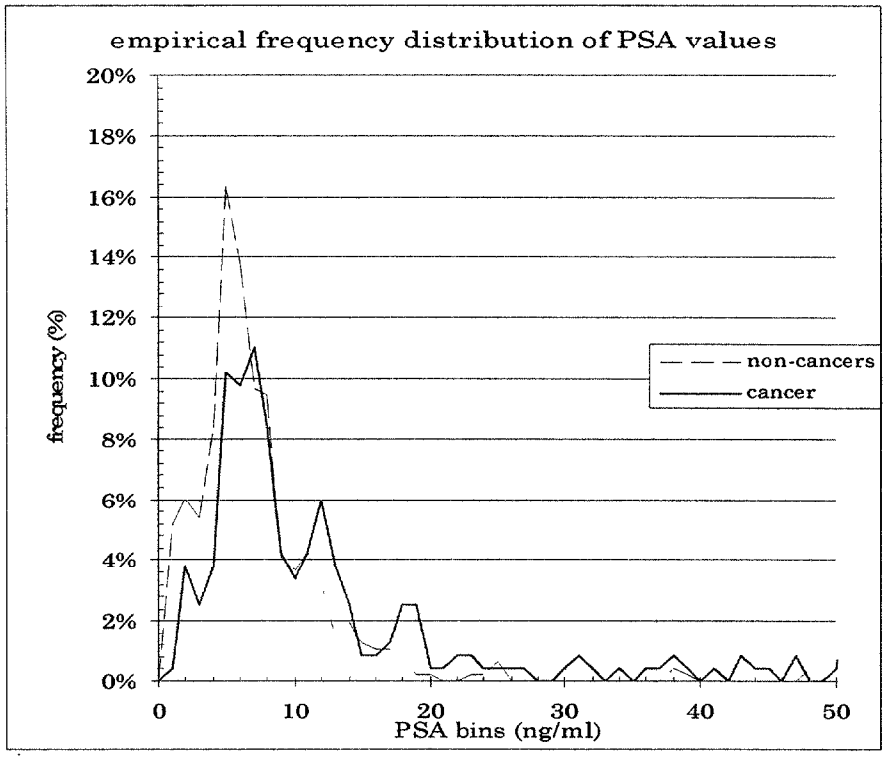
Biopsy result	count	%
Normal	186	26.6%
BPH	130	18.6%
PIN/Suspicious	42	6.0%
Prostatitis	107	15.3%
Malignant	235	33.6%

For analysis, all non-cancer results from biopsy were considered non-cancer. Of 234 cancer subjects with Gleason grading results available (one cancer subject lacked Gleason grading), 13% had Gleason grading of 4 or 5, 43% of subjects had Gleason grade 6, 33% had Gleason grade 7, and 11% had Gleason grade 8 or 9 cancers. Therefore, 76% of cancer subjects had Gleason grading of 6 or 7 and 89% had Gleason grading of 7 or less.

The mean PSA value for all subjects was 12.4 ng/ml ± 1.7 ng/ml (standard error of the mean). The mean PSA value of cancer subjects was 23.2 ng/ml ± 4.9 ng/ml (standard error of the mean) while the mean PSA value of non-cancer subjects was 6.9 ng/ml ± 0.3 ng/ml (standard error of the mean). The median PSA value of cancer subjects (8.0 ng/ml) was significantly different from the median PSA value of non-cancer subjects (5.6 ng/ml; $p < 0.001$ by Mann Whitney U test). Since the median PSA value of cancer is statistically different from non-cancer subjects, then it is possible to conclude that PSA results serve as one method of discriminating between cancer and non-cancer subjects.

Age and PSA results were marginally but statistically correlated with one another ($p = 0.0006$, Pearson correlation coefficient 0.130).

Though median and mean PSA values of cancer subjects is different from non-cancer subjects, the distribution of PSA values in each group has substantial overlap. The overlapping distributions are shown in the following graph of the empirical frequency distribution of PSA results among cancer and non-cancer subjects.



The graph illustrates a typical distribution of PSA results among men aged 50 years of age and older with and without cancer. The distribution of PSA values for both cancer and non-cancer subjects is skewed to the right and so is not normally distributed. As a result of the skewness, the mean and median values of both groups are significantly different from each other. The mean value of cancer subjects (23.2 ng/ml) is higher than the median value (8.0 ng/ml) and the mean value of non-cancer subjects (6.9 ng/ml) is higher than the median value (5.6 ng/ml).

2. Pooling of data by site

Data was collected for the clinical study of diseased patients from 34 sites throughout the United States. A rationale to assess the data from each site for poolability was evaluated using several patient characteristics and the performance of several diagnostic tests.

The first patient characteristic evaluated was the cancer rate by site. The rate ranged from 0% to 90% by site. Chi square analysis of the homogeneity of the cancer rate by site indicated significant differences ($p = 0.004$, Chi square value 58.157 for 33 degrees of freedom) from the pooled mean rate of 33.6%. The median cancer rate among the sites was 26.3% (binomial 95% confidence interval of the median 25.0% to 37.5%). Note that the pooled mean cancer rate, 33.6%, is contained within the 95% confidence interval of the median cancer rate by site, 25.0% to 37.5%. Graphical analysis of the frequency of the cancer rate indicated a significant skewing of values toward higher rates. Of the 34 sites, 15 had cancer rates higher than 40%. Analysis suggests that subjects evaluated at the sites

would appear to be different depending upon the section of the country in which the site is located.

The next patient characteristic evaluated was the rate of abnormal DRE by site. The rate ranged from 6% to 100% by site. Chi square analysis of the homogeneity of the rate of abnormal DRE by site indicated significant differences ($p < 0.0001$, Chi square value 97.778 for 33 degrees of freedom) from the pooled mean rate of 29.6%. The median abnormal DRE rate among the sites was 25% (binomial 95% confidence interval of the median 21.4% to 33.3%). Note that the pooled mean rate of abnormal DRE, 29.6%, is contained within the 95% confidence interval of the median rate by site. Graphical analysis of the frequency of rate of abnormal DRE indicated a significant skewing of values toward higher rates. Of the 34 sites, 13 had a rate of abnormal DRE higher than 40%. Analysis suggests that subjects evaluated at the sites would appear to be different depending upon the section of the country in which the site is located.

The next patient characteristic evaluated was the rate of elevated PSA (number of subjects with PSA >= 4.0 ng/ml) by site. The rate ranged from 50% to 100% by site. Chi square analysis of the homogeneity of the rate of elevated PSA by site indicated no significant differences ($p = 0.08$, Chi square value 44.937 for 33 degrees of freedom) from the pooled mean rate of 79.9%. The median rate of elevated PSA among the sites was 78.2% (binomial 95% confidence interval of the median 75.0% to 86.9%). Note that the pooled mean rate of elevated PSA, 79.9%, is contained within the 95% confidence interval of the median rate by site, 75.0% to 86.9%. Analysis suggests that subjects evaluated at the sites are not different depending upon the section of the country in which the site is located.

An evaluation of the test performance of three diagnostic tests by site was performed to determine if test performance was equivalent by site even though patients visiting the sites could be different. The first test performance evaluated was the odds of cancer given an abnormal DRE. The odds ratios of cancer given an abnormal DRE ranged from 0.20 to 10.33. The pooled odds ratio was 1.59. The mean odds ratio of cancer given an abnormal DRE by site was 1.83 (95% confidence interval 1.29 to 2.59). The probability that the mean odds ratio differed from the pooled odds ratio was 0.94. This indicates that the odds of cancer given an abnormal DRE did not differ significantly by site. Therefore, the use of DRE as a diagnostic test did not vary significantly by site.

The next test performance evaluated was the odds of cancer given an elevated PSA. The odds ratios of cancer given an elevated PSA ranged from 0.03 to 11.0. The pooled odds ratio was 2.79. The mean odds ratio of cancer given an elevated PSA by site was 1.94 (95% confidence interval 1.35 to 2.79). The probability that the mean odds ratio differed from the pooled odds ratio was 0.95. This indicates that the odds of cancer given an elevated PSA did not differ significantly by site. Therefore, the use of PSA as a diagnostic test did not vary significantly by site.

The next test performance evaluated was the odds of an abnormal DRE given an elevated PSA. The odds ratios of an abnormal DRE given an elevated PSA ranged from 0.10 to 2.78. The pooled odds ratio was 0.61. The mean odds ratio of an abnormal DRE given an elevated PSA by site was 0.62 (95% confidence interval 0.42 to 0.92). The probability that the mean odds ratio differed from the pooled odds ratio was 0.98. This indicates that the odds of an abnormal DRE given an elevated PSA did not differ significantly by site. Therefore, the use of PSA and DRE as a combined diagnostic test did not vary significantly by site.

Though 2 of 3 patient characteristics were significantly different by site, the pooled values of the test performance of DRE alone, PSA alone, and the combined use of PSA and DRE did not differ from the mean values by site. Analysis indicates that despite differing patient characteristics, the tests performed equivalently by site. Therefore, an analysis can be found supporting pooling and the data from the sites was pooled for final overall analysis.

3. Results of clinical study

DRE results and biopsy result (disease state) are cross-tabulated in the following table. The disease state Normal, BPH, prostatitis, and PIN/suspicious was combined into a benign disease state. The other disease state was malignancy. DRE result "not suspicious for cancer" was a combination of normal DRE (45.4% of tested subjects) and DRE not suspicious for cancer (25.0% of tested subjects) diagnoses. The DRE result "suspicious for cancer" was a combination of a DRE suspicious for cancer (19.4% of tested subjects) and "other" (10.1% of tested subjects) diagnoses. A DRE result of "suspicious for cancer" detected 36.2% of cancer subjects (85/235, 95% confidence interval 30.0% to 42.7%). A DRE result of "not suspicious for cancer" detected 73.8% of non-cancer subjects (343/465, 95% confidence interval 69.5% to 77.7%). The table is as follows:

Disease state	DRE result not suspicious for cancer	DRE result suspicious for cancer	Total
Malignant	150	85	235
Benign	343	122	465
Total	493	207	700

The positive predictive value of DRE alone was 0.411 ± standard error 0.034 (95% confidence interval 0.343 to 0.481). The negative predictive value of DRE alone was 0.696 ± standard error 0.021 (95% confidence interval 0.653 to 0.736). The probability that the PPV of DRE alone was equivalent with the prevalence was 0.015. DRE alone was better than a completely random test.

Of 700 subjects, 95% had PSA values less than 30 ng/ml. In subjects with malignant disease, 5% had PSA values less than 4.0 ng/ml. In subjects with benign disease, 20% had PSA values less than 4.0 ng/ml. PSA results and biopsy result (disease state) are cross-tabulated in the following table. The diseases normal, BPH, prostatitis, and PIN/Suspicious were combined into a benign disease state. The other disease state was malignant. The total PSA results were categorized as less than 4.0 ng/ml or ≥ 4.0 ng/ml). A PSA assay result ≥ 4.0 ng/ml deteted 89.4% of cancer subjects (210/235, 95% confidence interval 84.7% to 93.0%). A PSA result < 4 ng/ml detected 24.9% of non-cancer subjects (95% confidence interval 21.1% to 29.1%). The table is as follows:

Disease state	VIDAS TPSA < 4.0 ng/ml	VIDAS TPSA ≥ 4.0 ng/ml	Total
Malignant	25	210	235
Benign	116	349	465
Total	141	559	700

The positive predictive value of PSA alone was 0.376 ± standard error 0.021 (95% confidence interval 0.335 to 0.417). The negative predictive value of PSA alone was 0.823 ± standard error 0.032 (95% confidence interval 0.750 to 0.882). The probability that the PPV of PSA alone was equivalent with the prevalence was 0.029. PSA alone was better than a completely random test.

Receiver operator curve analysis was performed using the disease status to distinguish between cancer and non-cancer subjects. The area under the curve was 0.679 (95% confidence interval 0.637 to 0.722). The width of the confidence interval indicates that the area is significantly greater than 0.5.

To evaluate the combination of PSA results with DRE result, PSA values were categorized as < 4.0 ng/ml or ≥ 4.0 ng/ml while DRE results were categorized as not suspicious for cancer or suspicious for cancer. The folowing table presents the results as follows:

	DRE						
	Not suspicious for cancer			Suspicious for cancer			Total
Disease state	PSA < 4.0	PSA ≥ 4.0	Total	PSA < 4.0	PSA ≥ 4.0	Total	
Malignant	15	135	150	10	75	85	235
Benign	72	271	343	44	78	122	465
Total	87	406	493	54	153	207	700

A PSA result ≥ 4.0 ng/ml among subjects with a DRE result not suspicious for cancer detected 90.0% of cancer subjects (135/150, 95% confidence interval 84.0 to 94.3%) and for subjects with a DRE result suspicious for cancer 88.2% of cancer subjects (95% confidence interval 79.4% to 94.2%). The percentage of cancers detected by a PSA result ≥ 4.0 ng/ml is the same whether DRE result is suspicious for cancer or not.

The performance of the PSA assay in conjunction with DRE was determined. A positive PSA/DRE test result is described as either suspicious for cancer by DRE or when a PSA value ≥ 4.0 ng/ml or when both are positive. The following table summarizes the results:

Disease state	PSA/DRE result		Total
	Positive	Negative	
Malignant	220	15	235
Benign	393	72	465
Total	613	87	700

The combination of PSA and DRE detected 93.6% of cancer subjects (95% confidence interval 89.7% to 96.4%). The combination of PSA and DRE detected 15.5% of non-cancer subjects (95% confidence interval 12.3% to 19.1%).

A description of the added value of the PSA assay over the result from DRE alone was provided. The added value was defined as the increase in sensitivity directly attributable by the addition of PSA to the DRE result. There were 135 additional cancers identified by the combined use of PSA and DRE over DRE alone, an increased sensitivity of 57.4%. The addition of any random test to DRE alone will automatically increase the sensitivity and decrease the specificity of the combined use. For a random PSA test with a frequency of positive test results equal to 87.6% (613/700, equal to the frequency of a positive PSA test in this study), the number of cancer subjects detected by a positive result would be 91.7% ± standard error of 1.8%. The probability that the observed number of detected cancers, 93.6%, is equivalent with the expected number of detected cancers using a random test combined with DRE is 0.15. Therefore, the observed number of detected cancers is not significantly different from the expected number of cancers detected using any random test combined with DRE. Likewise, for a random PSA test with a frequency of a negative test result equal to 20.1% (141/700, equal to the frequency of a negative PSA test in this study), the number of non-cancer subjects detected by a negative result would be 14.9% ± standard error of 1.7%. The probability that the observed number of non-cancers detected by a negative test result, 15.5%, is equivalent with the expected number of non-cancer subjects with a negative test result using a random test combined with DRE is 0.35. Therefore, the observed number of detected cancers given a positive test result and the observed number of non-cancers detected given a negative test result for the combination of the PSA test with DRE do not differ from the calculated estimates

of a random PSA test used in combination with DRE when one or the other or both tests are positive.

The estimates of the probability (risk) of positive biopsy results are presented by the following table:

	Probability (Risk) of Positive Biopsy	95% CI
Pre-test	33.6% (235/700)	
DRE+	41.1% (85/207)	34.3% to 48.1%
DRE-	30.4% (150/493)	26.4% to 34.7%
PSA ≥ 4.0	37.6% (210/559)	33.5% to 41.7%
PSA < 4.0	17.7% (25/141)	11.8% to 25.1%
PSA ≥ 4.0 and DRE+	49.0% (75/153)	40.9% to 57.2%
PSA ≥ 4.0 and DRE -	33.3% (135/406)	28.7% to 38.1%
PSA < 4.0 and DRE+	18.5% (10/54)	9.3% to 31.4%
PSA < 4.0 and DRE -	17.2% (15/87)	10.0% to 26.8%
PSA ≥ 4.0 and DRE+ or PSA ≥ 4.0 and DRE – or PSA < 4.0 and DRE+	35.9% (220/613)	32.1% to 39.8%

The probability (risk) of positive biopsy represents the proportion of cancer subjects having the designated diagnostic test result.

The probability of positive biopsy for subjects with both an abnormal DRE and an elevated PSA was 49.0% (75/153) and the probability of positive biopsy for subjects with an abnormal DRE was 41.1% (85/207). The increase in the risk was 7.9% with 95% CI: 4.2% to 11.9%. The data demonstrated a statistically significant increase in the probabilities (risk) of positive biopsy for the subjects with an abnormal DRE and an elevated PSA results compared to the subjects with only abnormal DRE results.

The probability of positive biopsy for subjects with both a normal DRE and PSA < 4.0 ng/ml was 17.2% (15/87) and the probability of positive biopsy for DRE normal subjects was 30.4% (150/493). The decrease in the risks was 13.2% with 95% CI: 5.5% to 20.6%. The data demonstrated a statistically significant decrease in the probabilities (risk) of

positive biopsy for the subjects with normal DRE and PSA results < 4 ng/ml compared to the subjects with only normal DRE results. Because the sample of the biopsied subjects with normal DRE and PSA results < 4 ng/ml in the study may be not a representative sample from the population of male subjects with normal DRE and PSA results < 4 ng/ml, the estimate of the NPV(DRE OR PSA) can be potentially biased.

A cohort of 400 apparently healthy men aged 50 years or older having no fever or infections, meeting criteria for blood bank donation and who had no known prostate disease or history of prostate disease was evaluated using the PSA assay to determine the normal range and verify the clinically accepted cutoff of 4.0 ng/ml. Subjects also had a known age. The mean age was 63.7 years (95% CI 62.8 to 64.6 years). The median age was 62 years. Among the healthy cohort, 97.3% of subjects were Caucasian, 1.9% were other racial groups, and 6.8% had unknown racial category.

The normal healthy subjects were stratified into 3 groups approximately corresponding to age decade because PSA value may be age dependent. The following table shows the mean PSA, median, PSA, standard error of the mean, and subjects count by age decade among all 400 normal healthy subjects.

Age group	N	Mean (ng/ml)	Median (ng/ml)	Std error
50-59	155	1.40	0.94	0.12
60-69	135	1.70	0.99	0.14
70+	110	2.19	1.20	0.21

The 95% confidence intervals of the 95th percentile were estimated statistically by random re-sampling of the empirical distribution 10,000 times. The 95th percentile of the PSA result and the 95% confidence intervals are as follows:

	Age group 50-59	Age group 60-69	Age group 70+
95th percentile value	3.95 ng/ml	5.35 ng/ml	7.24 ng/ml
95% conf interval	2.49 – 4.84	4.09 – 6.58	6.00 – 9.35

In order to verify if the age and PSA result were correlated, 390 subjects with a verified age were analyzed by the Spearman rank correlation test. In this evaluation, known age was calculated from the difference in date of serum specimen collection and date of birth. From this calculation, a small number of subjects were re-categorized from the initial age decade categorization (9 subjects re-categorized). Ten subjects were excluded since they lacked a date of birth and date of specimen collection. In the Spearman rank correlation analysis, PSA and known age were modestly correlated ($p < 0.001$). The Spearman rank

correlation coefficient was 0.17 (95% confidence interval 0.07 to 0.26). The slope of the least squares correlation of PSA value vs. age indicates that the PSA value increases 0.03 ng/ml per year (slope = 0.034 ± standard error of 0.011). Over 10 years, the PSA value would increase 0.1 to 0.6 ng/ml.

Using a cutoff of 4.0 ng/ml, 93% of apparently healthy men aged 50 to 60 years of age had PSA values less than 4.0 ng/ml. Similarly, 88.5% of apparently healthy men aged 60 to 70 years of age had PSA values less than 4.0 ng/ml and 80% of apparently healthy men aged 70+ years had PSA values less than 4.0 ng/ml.

The lower 95% confidence interval for the 95th percentile value is 4.0 ng/ml within assay imprecision for subjects aged 50-59 years of age. Therefore, an appropriate cutoff based on the 95th percentile of normal subjects is 4.0 ng/ml. It is also accurate to state that a cutoff for older aged men would be correlated with their age and will be higher for men between 60-70 and greater than 70 years of age compared with men age 50-59.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

A. Safety

As a routine diagnostic test, the PSA assay involves removal of blood for testing purposes. The test, therefore, presents no more safety hazard than other tests where blood is removed from subjects.

B. Effectiveness

The VIDAS Total PSA is an effective in vitro quantitative assay to measure human serum PSA as an aid in the detection of prostate cancer when used in conjunction with DRE in men aged 50 years or older.

C. Risk Benefit Analysis

When the device is used according to the instructions provided, accurate assay results should be obtained. An error in the assay producing a falsely elevated PSA value could lead to an unnecessary biopsy. A falsely low PSA value could delay recognition of the presence of prostate cancer by the physician and could adversely delay the initiation of therapy.

An elevated PSA value is not diagnostic for prostate cancer. It should be used in conjunction with symptoms, clinical evaluation, digital rectal examination, and other diagnostic techniques. Confirmation of prostate cancer can only be determined by prostatic biopsy. Since the percentage of subjects falsely identified as free of cancer using prostate tissue from six cores is approximately 25% on first sampling, the presence of an elevated total PSA may fail to detect prostate cancer on first biopsy sampling. Physicians

and patients should keep in mind the risks of failure to detect cancer when a negative biopsy result (absence of cancer) is received.

When both PSA is greater than 4.0 ng/ml and a DRE examination is abnormal suspicious for cancer, the least number of false positive subjects is present. The number of cancers detected was 88% of the cancers detected by DRE alone while the number of false positives detected was 64% of the false positives detected by DRE alone. In the current study, the probability of cancer given this test situation is greater than 41%. When one or the other or both PSA and DRE were positive in this study, 2.6 times as many cancer subjects were detected in this test situation as detected by DRE alone. However, the number of false positives was 3.2 times higher than the false positive rate of DRE alone. In the current study, the probability of cancer given a positive DRE or elevated PSA or both was 36%.

It is reasonable to conclude that the benefits of use of the device for the target population outweigh the risk of illness or injury when used in accordance with the directions for use.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Immunology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval order on July 8, 2004.

The applicant's manufacturing facility inspected on November 27, 2003 and found to be in compliance with the device Quality System regulations (21 CFR part 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Warnings and Precautions in the labeling.

Post approval requirements:See Approval order.

XV. REFERENCES

1. McCormack RT, Rittenhouse HG, Finlay JA, *et al.* Molecular Forms of Prostate-Specific Antigen and the Human Kallikrein Gene Family: A New Era. *Urology* 1995; 45:729–44.

2. Chan DW, Bruzek DJ, Oesterling JE, *et al.* Prostate-Specific Antigen as a Marker for Prostatic Cancer: A Monoclonal and A Polyclonal Immunoassay Compared. *Clin Chem* 1987; 33:1916–20.

3. Hortin GL, Bahnson RR, Daft M, *et al.* Differences In Values Obtained With 2 Assays of Prostate Specific Antigen. *J Urol* 1988; 139:762–5.